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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [5]: C07C 323/63, 237/42, 233/54 A61K 31/195, C07C 237/44 A61K 31/165, 31/145	A2	(11) International Publication Number: WO 92/03412 (43) International Publication Date: 5 March 1992 (05.03.92)

(21) International Application Number: PCT/GB91/01375

(22) International Filing Date: 13 August 1991 (13.08.91)

(30) Priority data:
9017711.4 13 August 1990 (13.08.90) GB

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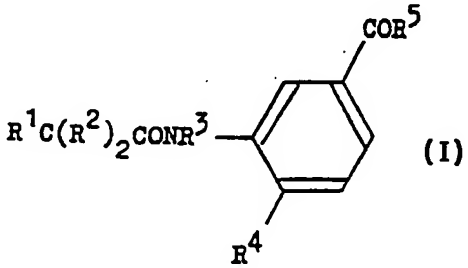
(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, PL, SE (European patent), SU+,US.

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: BENZAMIDE DERIVATIVES



(I)

(57) Abstract

A benzamide derivative of formula (I) wherein R^1 represents alkyl optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms, or sulphinyl or sulphonyl groups, optionally carrying one or more substituents selected from halogen, amino, alkoxy, alkylthio, alkylamino, or -$CONR^6R^7$ groups wherein R^6 represents hydrogen or methyl and R^7 represents methyl, trifluoromethyl or trichloromethyl, the symbols R^2 represent hydrogen, alkyl or optionally substituted phenyl or the two groups R^2 form a ring, R^3 represents hydrogen or alkyl, R^4 represents alkoxy, alkylthio, dimethylamino, or a 5- to 8-membered heterocyclo group, and R^5 represents -NR^8R^9 or -OR^{10} wherein R^8 and R^9 represents hydrogen or alkyl optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms, or sulphinyl or sulphonyl groups, and R^{10} represents hydrogen or alkyl optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms, or sulphinyl or sulphonyl groups, and pharmaceutically acceptable salts thereof, possess useful pharmacological properties.

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BENZAMIDE DERIVATIVES

This invention relates to new, therapeutically useful benzamide derivatives, to a process for their production and to pharmaceutical compositions containing them, and methods for their use.

The new benzamide derivatives of the present invention are the compounds of formula I, hereinafter depicted, wherein R^1 represents a straight- or branched-chain alkyl group containing up to about 20 carbon atoms, optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms, e.g. oxygen, sulphur or nitrogen atoms, and optionally interrupted by one or more sulphinyl or sulphonyl groups, preferably an alkylthioalkyl, alkylaminoalkyl or dialkylaminoalkyl group or more especially an alkyl, alkenyl, alkoxyalkyl, alkoxyalkoxyalkyl, or alkoxyalkoxyalkoxyalkyl group, optionally carrying one or more substituents selected from halogen, e.g. bromine, iodine, fluorine or, preferably, chlorine, atoms, amino groups, alkoxy, alkylthio and alkylamino groups each containing up to about 3 carbon atoms, and groups of the formula $-CONR^6R^7$ wherein R^6 represents a hydrogen atom or a methyl group and R^7 represents a methyl, trifluoromethyl or trichloromethyl group, the symbols R^2 are the same or different and each

represents a hydrogen atom, a straight- or branched-chain alkyl group containing up to about 6 carbon atoms or an optionally substituted phenyl group or the two groups R^2 together with the carbon atom to which they are attached form a saturated or unsaturated ring containing from 3 to about 8 carbon atoms and optionally containing one or more hetero atoms selected from oxygen, sulphur and nitrogen atoms, R^3 represents a hydrogen atom or a straight- or branched-chain alkyl group containing up to about 6 carbon atoms, R^4 represents a straight- or branched-chain alkoxy or alkylthio group containing up to about 6 carbon atoms or a dimethylamino group or a 5- to 8-membered heterocyclo group containing at least one nitrogen atom and linked via that nitrogen atom to the rest of the molecule, e.g. an imidazol-1-yl or pyrrolidin-1-yl group, and R^5 represents a group of the formula $-NR^8R^9$ or $-OR^{10}$ wherein R^8 and R^9 may be the same or different and each represents a hydrogen atom or a straight- or branched-chain alkyl group containing up to about 10 carbon atoms, optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms, e.g. oxygen, sulphur or nitrogen atoms, and optionally interrupted by one or more sulphinyl or sulphonyl groups, and R^{10} represents a hydrogen atom or a

straight- or branched-chain alkyl group containing up to about 10 carbon atoms, optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms, e.g. oxygen, sulphur or nitrogen atoms, and optionally interrupted by one or more sulphinyl or sulphonyl groups, and pharmaceutically acceptable salts thereof.

As will be apparent to those skilled in the art, some of the compounds of formula I exhibit optical isomerism. All such forms, and their mixtures, and processes for their preparation and separation, are embraced by the invention.

Especially important compounds of the present invention include those wherein at least one of the symbols has a value selected from the following:-

(i) R^1 represents an alkyl, alkenyl, alkoxyalkyl, alkoxyalkoxyalkyl, alkoxyalkoxyalkoxyalkyl or haloalkyl, e.g. chloroalkyl, group, containing from 8 to 20 carbon atoms, preferably an alkyl or alkenyl group containing from 8 to 20, preferably 10 to 18, carbon atoms;

(ii) the symbols R^2 each represent a hydrogen atom, or the two groups R^2 together with the carbon atom to which they are attached form a cycloalkyl ring containing from 3 to 8, preferably 5 or 6, e.g. 5, carbon atoms;

(iii) R^3 represents a hydrogen atom;

(iv) R^4 represents an imidazol-1-yl group or a straight- or branched-chain alkoxy or alkylthio group containing up to 3, preferably 1 or 2, carbon atoms, preferably methoxy, methylthio or ethylthio;

(v) R^8 represents a hydrogen atom or a straight- or branched-chain alkyl group containing up to 3 carbon atoms, e.g. methyl;

(vi) R^9 represents a straight- or branched-chain alkyl or alkenyl group containing up to 6 carbon atoms, optionally interrupted by one or more oxygen or sulphur atoms or sulphonyl groups, preferably an alkyl, alkoxyalkyl or alkylthioalkyl group containing 3 or 4 carbon atoms, or an alkenyl group containing 5 carbon atoms, e.g. a butyl, methoxyethyl, methylthioethyl, methoxypropyl, methylthiopropyl, methylsulphonylpropyl or methylbut-2-enyl group;

(vii) R^{10} represents a hydrogen atom or a straight- or branched-chain alkyl group containing up to 6, preferably up to 3, carbon atoms, e.g. methyl;

the other symbols being as hereinbefore defined, and pharmaceutically acceptable salts thereof.

Important compounds according to the invention include:-

A (Z)-N-(2-methylthio)ethyl-4-methylthio-3-(octadec-9-enamido)benzamide ;

B (Z)-N-(2-methoxy)ethyl-4-methylthio-3-(octadec-9-enamido)benzamide;

C (Z)-methyl 4-methoxy-3-(octadec-9-enamido)-benzoate;

D N-(2-methylthio)ethyl-3-hexadecanamido-4-(methylthio)benzamide;

E N-butyl-3-hexadecanamido-4-(methylthio)benzamide;

F N-(2-methoxy)ethyl-3-hexadecanamido-4-(methylthio)benzamide;

G N-butyl-3-dodecanamido-4-(methylthio)benzamide;

H N-(2-methoxy)ethyl-3-dodecanamido-4-(methylthio)benzamide;

I N-(2-methylthio)ethyl-3-dodecanamido-4-(methylthio)benzamide;

J N-butyl-N-methyl-3-hexadecanamido-4-methoxybenzamide;

K (Z)-N-butyl-4-methoxy-3-(octadec-9-enamido)-benzamide;

L N-(2-methylthio)ethyl-3-(1-decylcyclopentanecarboxamido)-4-(methylthio)benzamide;

M (Z)-sodium 4-methoxy-3-(octadec-9-enamido)-benzoate;

N (Z)-4-methoxy-3-(octadec-9-enamido)benzoic acid;

O N-butyl-3-dodecanamido-4-(ethylthio)benzamide;

P N-butyl-4-ethylthio-3-hexadecanamidobenzamide;

Q N-butyl-4-ethylthio-3-heptadecanamidobenzamide;

R N-butyl-4-ethylthio-3-octadecanamidobenzamide;

S 4-ethylthio-3-hexadecanamido-N-(2-methylthio-ethyl)benzamide;

T 4-ethylthio-3-heptadecanamido-N-(2-methylthio-ethyl)benzamide;

U 3-heptadecanamido-4-methylthio-N-(2-methylthio-ethyl)benzamide;

V 3-heptadecanamido-N-(2-methoxyethyl)-4-(methyl-thio)benzamide;

W (Z)-N-butyl-3-octadec-9-enamido-4-(methylthio)-benzamide;

X 4-ethylthio-N-(3-methylthiopropyl)-3-octa-decanamidobenzamide;

Y 4-ethylthio-3-heptadecanamido-N-(3-methylthio-propyl)benzamide;

Z 4-ethylthio-3-hexadecanamido-N-(3-methylthio-propyl)benzamide;

AA 4-methylthio-N-(2-methylthioethyl)-3-octa-decanamidobenzamide;

AB N-butyl-3-dodecanamido-4-methoxybenzamide;

AC 4-ethylthio-3-hexadecanamido-N-(3-methoxy-propyl)benzamide;

AD N-butyl-3-octadecanamido-4-(methylthio)-

benzamide;

AE 4-methylthio-N-(3-methylthiopropyl)-3-octadecanamidobenzamide;

AF 4-ethylthio-N-(3-methoxypropyl)-3-octadecanamidobenzamide;

AG N-butyl-3-(5-chloropentanamido)-4-(ethylthio)-benzamide;

AH 3-(4-chlorobutanamido)-4-ethylthio-N-(3-methylthiopropyl)benzamide;

AI 3-(5-chloropentanamido)-4-ethylthio-N-(3-methylthiopropyl)benzamide;

AJ methyl 3-hexadecanamido-4-methoxybenzoate;

AK 3-hexadecanamido-4-methoxybenzoic acid;

AL sodium 3-hexadecanamido-4-methoxybenzoate;

AM 3-hexadecanamido-4-methoxy-N-(2-methoxyethyl)-benzamide;

AN 3-hexadecanamido-4-methoxy-N-(3-methylbut-2-enyl)benzamide;

AO N-butyl-4-methylthio-3-(5,9-dioxahexadecanamido)benzamide;

AP 4-methylthio-N-(3-methylthiopropyl)-3-(5,9-dioxahexadecanamido)benzamide;

AQ N-butyl-4-ethylthio-3-(5,9,13-trioxahexadecanamido)benzamide;

AR 4-ethylthio-N-(3-methylthiopropyl)-3-(5,9-dioxahexadecanamido)benzamide;

AS N-butyl-4-ethylthio-3-(5,9-dioxahexadecanamido)benzamide;

AT 4-ethylthio-N-(3-methoxypropyl)-3-(5,9-dioxahexadecanamido)benzamide;

AU 4-ethylthio-N-(3-methoxypropyl)-3-(5,9,13-trioxahexadecanamido)benzamide;

AV 4-ethylthio-N-(3-methoxypropyl)-3-(5-oxahexadecanamido)benzamide;

AW 4-methylthio-N-(3-methylthiopropyl)-3-(5-oxahexadecanamido)benzamide;

AX N-butyl-4-methylthio-3-(5-oxahexadecanamido)-benzamide;

AY 4-methoxy-N-(3-methylthiopropyl)-3-(5,9-dioxahexadecanamido)benzamide;

AZ 4-ethylthio-N-(3-methylthiopropyl)-3-(5,9,13-trioxahexadecanamido)benzamide;

BA methyl 3-heptadecanamido-4-(imidazol-1-yl)-benzoate;

BB N-(3-methylsulphonylpropyl)-4-methylthio-3-(5,9-dioxahexadecanamido)benzamide;

BC 4-ethylthio-N-(3-methylthiopropyl)-3-(5,9-dioxaoctadecanamido)benzamide;

BD N-butyl-4-ethylthio-3-(5,10-dioxahexadecanamido)benzamide;

BE 4-ethylthio-N-(3-methylthiopropyl)-3-(6,10,14-trioxahexadecanamido)benzamide;

BF 4-imidazol-1-yl-N-(3-methylthiopropyl)-3-(5-oxahexadecanamido)benzamide; and

BG 3-hexadecanamido-4-imidazol-1-yl-N-(3-methylthiopropyl)benzamide.

The letters A to BG are allocated to compounds for easy reference later in this specification.

The compounds according to the invention are inhibitors of acyl coenzyme-A:cholesterol-O-acyl transferase (ACAT;EC 2.3.1.26). They are therefore of value as anti-atherosclerotic agents and have utility in the treatment of atherosclerosis, hyperlipidaemia, cholesterol ester storage disease and atheroma in vein grafts.

Compounds within the scope of the present invention exhibit positive pharmacological activities as demonstrated by the following in vitro and in-vivo tests which are believed to correlate to pharmacological activity in humans and other animals.

In assays performed in vitro microsomes (prepared from the livers of rats fed a diet supplemented with 0.5%w/w cholesterol and 0.25%w/w cholic acid for 7 days) were incubated with radiolabelled oleoyl-CoA in the presence of compounds according to the invention at a concentration of 0.5μg/ml or 1μg/ml. The degree of ACAT inhibition produced was up to 99%.

In in-vivo tests, using rats fed on a diet similar to that described above and supplemented further by 0.01%w.w of test compound, compounds according to the invention inhibited increases in plasma cholesterol concentrations, measured after 3 days, relative to control animals fed on the cholesterol supplemented diet without the drug, by up to 100%.

Compounds of formula I can be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature.

According to a feature of the present invention, compounds of general formula I are prepared by the reaction of a compound of general formula II hereinafter depicted, wherein R^3, R^4 and R^5 are as hereinbefore defined, with a compound of the general formula:

$$R^1\text{-}C(R^2)_2COZ^1 \qquad \text{(III)}$$

wherein R^1 and R^2 are as hereinbefore defined and Z^1 represents a halogen, e.g. chlorine, atom or an alkoxycarbonyloxy group, for example methoxycarbonyloxy or ethoxycarbonyloxy, or with the corresponding anhydride of the general formula:

$$[R^1\text{-}C(R^2)_2CO]_2O \qquad \text{(IV)}$$

wherein R^1 and R^2 are as hereinbefore defined.

When Z^1 represents a halogen atom the reaction may be performed in the presence of a suitable base, such as a tertiary amine, e.g. triethylamine or pyridine.

In each instance the reaction may be carried out in a suitable solvent, e.g. dichloromethane, optionally with heating.

According to a further feature of the invention, compounds of formula I wherein R^{10} is other than hydrogen are prepared by reacting a compound of general formula:

$$R^{11}OH \qquad (V)$$

wherein R^{11} represents a straight- or branched-chain alkyl group containing up to about 10 carbon atoms, optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms, e.g. oxygen, sulphur or nitrogen atoms, and optionally interrupted by one or more sulphinyl or sulphonyl groups, or a compound of general formula:

$$HNR^8R^9 \qquad (VI)$$

wherein R^8 and R^9 are as hereinbefore defined, with a compound of formula VII, hereinafter depicted, wherein R^1, R^2, R^3 and R^4 are as hereinbefore defined and Z^2 represents a hydroxy group, a halogen, e.g. chlorine, atom or an alkoxycarbonyloxy group, for example methoxycarbonyloxy or ethoxycarbonyloxy, or with the corresponding anhydride .

The reaction conditions are similar to those described above for the reaction between the compounds of general formulae II and III.

When Z^2 represents a hydroxy group the reaction is preferably performed in the presence of a condensing

agent, such as dicyclohexylcarbodiimide, or a catalytic quantity of an inorganic acid, e.g. hydrochloric acid, optionally prepared in situ.

In each instance the reaction may be carried out in a suitable solvent, e.g. dichloromethane, optionally with heating.

According to a further feature of the invention, compounds of general formula I are prepared by the interconversion of other compounds of formula I. For example, according to a feature of the invention, (a) compounds of formula I wherein R^3 and/or R^8 and/or R^9 is other than a hydrogen atom are prepared from compounds of formula I wherein R^3 and/or R^8 and/or R^9 represents a hydrogen atom by the application or adaptation of known methods of alkylation; according to a further feature of the invention, (b) compounds of formula I containing a sulphonyl group are prepared by the oxidation of compounds of formula I containing a sulphinyl or thio group and compounds of formula I containing a sulphinyl group are prepared by the oxidation of compounds of formula I containing a thio group using a conventional oxidant, such as a percarboxylic acid (e.g. m-chloroperbenzoic acid), in an inert solvent, such as dichloromethane, at or below room temperature; according to a further feature of the invention, (c) compounds of formula I wherein R^{10}

represents a hydrogen atom are prepared from compounds of formula I wherein R^{10} represents a straight- or branched-chain alkyl group containing up to about 10 carbon atoms, optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms, e.g. oxygen, sulphur or nitrogen atoms, and optionally interrupted by one or more sulphinyl or sulphonyl groups, by hydrolysis of the ester grouping $-COOR^{10}$ by known methods, for example by reaction with alkali, e.g. aqueous sodium hydroxide solution, followed by neutralisation by treatment with mineral acid, e.g. dilute hydrochloric acid; and, conversely, according to a further feature of the invention, (d) compounds of formula I wherein R^{10} represents a straight- or branched-chain alkyl group containing up to about 10 carbon atoms, optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms, e.g. oxygen, sulphur or nitrogen atoms, and optionally interrupted by one or more sulphinyl or sulphonyl groups are prepared by the esterification of compounds of formula I wherein R^{10} represents a hydrogen atom, by the application or adaptation of known methods.

By the term "pharmaceutically acceptable salts" as used in this specification is meant acid addition

salts the anions of which are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial pharmaceutical properties of the compounds of formula I are not vitiated by side-effects ascribable to those anions and salts formed with bases such as alkali metal, e.g. sodium or potassium, salts and alkaline earth metal, e.g. calcium or magnesium, salts, the cations of which are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial pharmaceutical properties of the compounds of formula I are not vitiated by side-effects ascribable to those cations.

It is to be understood that, where in this specification reference is made to the compounds of formula I, it is intended to refer also, where the context so permits, to their pharmaceutically acceptable salts.

Suitable acid addition salts for use in pharmaceuticals may be selected from salts derived from inorganic acids, for example hydrochlorides, hydrobromides, phosphates, sulphates and nitrates, and organic acids, for example oxalates, lactates, tartrates, acetates, salicylates, citrates, propionates, succinates, fumarates, maleates, methylene-bis-ß-hydroxynaphthoates, gentisates and di-p-toluoyltartrates.

As well as being useful in themselves as active compounds, salts of the compounds of formula I are useful for the purposes of purification of the parent compounds, for example by exploitation of the solubility differences between the salts and the parent compound, by techniques well known to those skilled in the art.

The salts can be prepared from the parent compounds of formula I by the application or adaptation of known methods, and the parent compounds of formula I can be prepared from the salts by the application or adaptation of known methods.

The compounds of formula I can be purified by the usual physical means, for example by crystallisation or chromatography.

Compounds of formulae II, III, IV, V, VI and VII may be prepared by the application or adaptation of known methods.

For example, acid halides of formula VII wherein Z^1 represents a halogen atom may be prepared from the corresponding carboxylic acids of formula VII wherein Z^1 represents a hydroxy group by the application or adaptation of known methods, e.g., when Z^1 represents a chlorine atom, by reaction with thionyl chloride or oxalyl chloride.

Similarly, acid halides of formula III wherein Z^1 represents a halogen atom may be prepared from the corresponding carboxylic acids of the general formula:-

$$R^1\text{-}C(R^2)_2COOH \quad (VIII)$$

wherein R^1 and R^2 are as hereinbefore defined, by the application or adaptation of known methods, e.g., when Z^1 represents a chlorine atom, by reaction with thionyl chloride or oxalyl chloride.

Compounds of the general formula:-

$$R^{12}\text{-}C(R^2)_2COOH \quad (IX)$$

within formula VIII, wherein R^{12} represents an alkoxyalkyl or, more particularly, an alkoxyalkoxyalkyl or, especially, an alkoxyalkoxyalkoxyalkyl, group, and R^2 is as hereinbefore defined, are key intermediates and they, a process for their preparation, and their use in synthesis of useful pharmaceuticals, e.g. compounds of formula I, form features of the present invention.

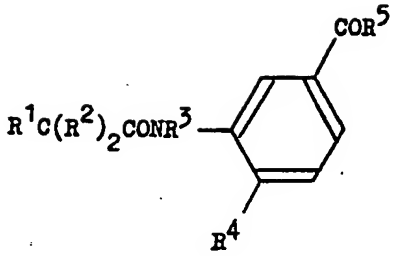
According to a feature of this invention, compounds of formula IX are prepared by the oxidation of compounds of the general formula:-

$$R^{12}\text{-}C(R^2)_2CH_2OH \quad (X)$$

wherein R^{12} and R^2 are as hereinbefore defined, by the application or adaptation of known methods, for example by reaction with an alkali metal halite such as sodium bromite and a free radical such as 2,2,6,6-tetramethyl-

1-piperidinyloxy free radical.

This reaction is preferably carried out in the presence of a base such as an aqueous solution of an alkali metal carbonate or bicarbonate, and in the presence of a suitable solvent such as acetonitrile, preferably at or, more especially below room temperature.



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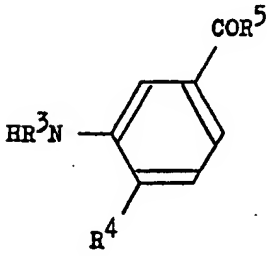

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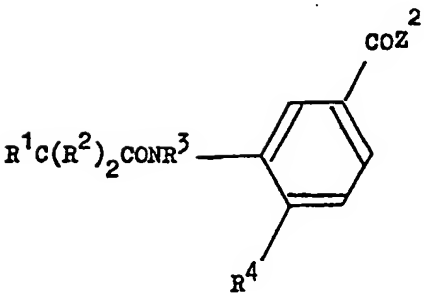


VII

The following Examples illustrate the preparation of the compounds according to the invention. Examples 1 to 16 illustrate the preparation of compounds of general formula I, Examples 17 and 18 illustrate the preparation of key intermediates of general formula IX, and the Reference Examples illustrate the preparation of other intermediates.

EXAMPLE 1

Compound A

A stirred solution of oleic acid (4.20g) and triethylamine (1.8g) in dichloromethane (50ml was treated with methyl chloroformate (1.7g) at -30°C. The mixture was stirred for 2 hours, allowing it to warm to the ambient temperature. It was then treated with a solution of N-(2-methylthio)ethyl-4-methylthio-3-aminobenzamide (4.0g) and triethylamine (2.5g) in dichloromethane (50ml). The resulting clear solution was left to stand for 17 hours and was then diluted with dichloromethane (250ml), washed sequentially with hydrochloric acid (200ml;1N), aqueous sodium chloride solution, saturated aqueous sodium hydrogen carbonate solution (100ml) and finally with aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. The resulting residue was dissolved in diethyl ether (250ml) and the

solution was washed with hydrochloric acid (2x150ml;2N), dried over magnesium sulphate and concentrated under reduced pressure. The resulting residue was crystallised from a mixture of petrol (b.p. 40-60°C) and diethyl ether, to give a waxy solid, which was subjected to column chromatography on silica gel, eluting with ethyl acetate, and recrystallised from t-butyl methyl ether, to give (Z)-N-(2-methylthio)ethyl-4-methylthio-3-(octadec-9-enamido)benzamide (0.7g) in the form of a colourless, soft solid, m.p. 84-86°C. [Elemental analysis:-C,67.4;H,9.5;N,5.1; S,12.2%; calculated:- C,66.88;H,9.29;N,5.38;S,12.31%].

EXAMPLE 2

Compound B

An ice-cooled solution of N-(2-methoxy)ethyl-3-amino-4-(methylthio)benzamide (3.99g) in dry dichloromethane (50ml) and dry triethylamine (2.79ml) was slowly treated with a solution of oleoyl chloride (5g) in dry dichloromethane (30ml). The mixture was stirred at the ambient temperature for 2.5 hours and was then concentrated under reduced pressure, to leave a solid. This solid was dissolved in ethyl acetate and the solution was washed sequentially with hydrochloric acid (2N), aqueous sodium hydroxide solution (1N) and with water, dried over magnesium sulphate and concentrated under reduced pressure.

The resulting residue was crystallised from a mixture of amyl acetate (65ml) and ethyl acetate (5ml), and then from toluene, to give (Z)-N-(2-methoxy)ethyl-4-methylthio-3-(octadec-9-enamido)benzamide (4.81g) in the form of a soft, white solid, m.p. 110-112°C. [Elemental analysis:- C,69.1;H,9.8;N,5.46;S 6.5%; calculated:- C,69.00;H,9.58;N,5.55;S,6.35%].

EXAMPLE 3

Compound C

A solution of methyl 3-amino-4-methoxybenzoate (3.0g) in dry dichloromethane (50ml) and dry triethylamine (2.79ml) was slowly treated with a solution of oleoyl chloride (5g) in dry dichloromethane (30ml). The mixture was stirred at the ambient temperature for 45 minutes and was then concentrated under reduced pressure. The resulting solid was crystallised from aqueous ethanol, to give brown crystals (6.63g), of which a sample (250mg) was recrystallised from ice-cold petrol (b.p. 40-60°C) containing a trace of methanol, to give (Z)-methyl 4-methoxy-3-(octadec-9-enamido)benzoate (195mg), in the form of off-white crystals, m.p. 46-47°C. [Elemental analysis:- C,72.2;H,9.65;N,3.18%; calculated:- C,72.77; H,9.72;N,3.14%].

EXAMPLE 4

Compound K

A stirred, ice-cooled solution of (Z)-4-methoxy-3-(octadec-9-enamido)benzoyl chloride (1.5g) [prepared by the reaction of thionyl chloride with (Z)-4-methoxy-3-(octadec-9-enamido)benzoic acid (itself prepared as described hereinafter in Example 7)] in dichloromethane (20ml) was treated with a solution of butylamine (0.5g) in dry dichloromethane (10ml). The mixture was stirred at the ambient temperature for 1 hour and was then concentrated under reduced pressure. The resulting residue was crystallised from cyclohexane and then recrystallised from a mixture of diethyl ether and pentane to give (Z)-N-butyl-4-methoxy-3-(octadec-9-enamido)benzamide (0.474g) in the form of a grey solid, m.p. 81-82°C. [Elemental analysis:- C,73.9;H,10.4; N,5.7%; calculated:- C,74.03;H,10.35;N,5.76%].

EXAMPLE 5

Compounds D, E, F, G, H, I and J

A solution of N-(2-methylthio)ethyl-3-amino-4-(methylthio)benzamide (3.0g) and dry triethylamine (3.0g) in dry dichloromethane (50ml) was treated with a solution of hexadecanoyl chloride (3.4g) in dry dichloromethane (20ml). The solution was stirred at the ambient temperature for 3 hours and was then diluted with dichloromethane (250ml). The solution

was washed with hydrochloric acid (100ml;1N), dried over magnesium sulphate and concentrated under reduced pressure, and the resulting solid was recrystallised from a mixture of t-butyl methyl ether and ethanol (9:1v/v), to give N-(2-methylthio)ethyl-3-hexadecanamido-4-(methylthio)benzamide (5.14g) in the form of white crystals, m.p. 104-105°C. [Elemental analysis:- C,65.3;H,9.4;N,5.6;S,13.2%; calculated:- C,65.54;H,9.37;N,5.66;S,12.96%].

By proceeding in a similar manner, but using the appropriate acid chloride and the appropriate aminobenzamide derivative, there were prepared:- N-butyl-3-hexadecanamido-4-(methylthio)benzamide,in the form of white crystals, m.p. 125-126°C [Elemental analysis:- C,70.4;H,10.18;N,5.88;S,6.95%; calculated:- C,70.54;H,10.15;N,5.88;S,6.73%]; N-(2-methoxy)ethyl-3-hexadecanamido-4-(methylthio)-benzamide in the form of white crystals, m.p. 115-117°C [Elemental analysis:- C,68.1;H,9.9;N,5.8;S,6.88%; calculated:- C,67.74;H,9.69;N,5.85;S,6.70%]; N-butyl-3-dodecanamido-4-(methylthio)benzamide in the form of white crystals, m.p. 126-128°C [Elemental analysis:- C,68.4;H,9.6;N,6.7;S,7.7%; calculated:- C,68.53;H,9.58;N,6.66;S,7.62%]; N-(2-methoxy)ethyl-3-dodecanamido-4-(methylthio)-

benzamide in the form of white crystals, m.p. 113-115°C [Elemental analysis:- C,65.3;H,9.2;N,6.6;S,7.6%; calculated:- C,65.37;H,9.06;N,6.63;S,7.59%]; N-(2-methylthio)ethyl-3-dodecanamido-4-(methylthio)-benzamide in the form of white needles, m.p. 102-104°C [Elemental analysis:- C,63.1;H,8.8;N,6.7;S,14.7%; calculated:- C,62.97;H,8.73;N,6.39;S,14.62%]; and N-butyl-N-methyl-3-hexadecanamido-4-methoxybenzamide in the form of an off-white powder [from petrol (b.p. 100-120°C)], m.p. 66-68°C [Elemental analysis:- C,73.2; H,10.8;N,5.61%; calculated:- C,73.37;H,10.62;N,5.90%].

EXAMPLE 6

Compound L

A solution of 1-decylcyclopentanecarboxylic acid (2.1g) and thionyl chloride (3ml) in dry dichloromethane (30ml) was heated at reflux for 3 hours. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in dichloromethane (30ml) and added to a solution of dry triethylamine (2.4g) and N-(2-methylthio)ethyl-3-amino-4-(methylthio)benzamide (2.16g) in dichloromethane (50ml). The mixture was stirred at the ambient temperature for 1 hour, then it was diluted with dichloromethane (100ml) and washed sequentially with hydrochloric acid (100ml;1N), aqueous sodium chloride solution (100ml), aqueous potassium hydroxide solution

(1.5g in 100ml), hydrochloric acid (100ml;1N) and with aqueous sodium chloride solution (100ml), dried over magnesium sulphate and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel, eluting with t-butyl methyl ether, to give N-(2-methylthio)ethyl-3-(1-decylcyclopentane-carboxamido)-4-(methylthio)benzamide (3.15g) in the form of a waxy solid.

[Elemental analysis:- C,66.2;H,9.4;N,5.24;S,12.3%; calculated for $C_{27}H_{44}N_2O_2S_2$:1/3:$C_5H_{12}O$:- C,65.94;H,9.27;N,5.36;S,12.28%].

EXAMPLE 7

Compounds M and N

A mixture of (Z)-methyl 4-methoxy-3-(octadec-9-enamido)benzoate (6.12g; prepared as described in Example 3), sodium hydroxide (0.6g), water (20ml) and ethanol (200ml) was heated at reflux for 1.5 hours. The mixture [containing (Z)-sodium 4-methoxy-3-(octadec-9-enamido)benzoate] was cooled to the ambient temperature and was then poured onto a mixture of crushed ice and concentrated hydrochloric acid. The product was collected and recrystallised from methanol, to give (Z)-4-methoxy-3-(octadec-9-enamido)benzoic acid (4.14g) in the form of a white powder, m.p. 179-183°C. [Elemental analysis:- C,72.3;H,9.5; N,3.3%; calculated:- C,72.35;H,9.57;N,3.24%].

EXAMPLE 8

Compounds O to V

By proceeding in a manner similar to that described in Example 5, but employing the appropriate acid chlorides and the appropriate anilines, and simply removing the solvent under reduced pressure at the end of the reaction period and crystallising the residue , there were prepared:-

N-butyl-3-dodecanamido-4-(ethylthio)benzamide, in the form of white plates, m.p. 102-104°C (from aqueous ethanol) [Elemental analysis:- C,69.0;H,9.9;N,6.4; S,7.4%; calculated:- C,69.08;H,9.74;N,6.45;S,7.37%];

N-butyl-4-ethylthio-3-hexadecanamidobenzamide, in the form of white crystals, m.p. 89-91°C (from aqueous ethanol) [Elemental analysis:- C,70.9;H,10.3;N,5.4; S,6.57%; calculated:- C,70.97;H,10.27;N,5.71;S,6.53%];

N-butyl-4-ethylthio-3-heptadecanamidobenzamide, in the form of white crystals, m.p. 81-83°C (from aqueous ethanol) [Elemental analysis:- C,71.1;H,10.7;N,5.3; S,6.09%; calculated:- C,71.37;H,10.38;N,5.55;S,6.35%];

N-butyl-4-ethylthio-3-octadecanamidobenzamide, in the form of white crystals, m.p. 80-82°C (from aqueous ethanol) [Elemental analysis:- C,71.6;H,10.8;N,5.3; S,6.02%; calculated:- C,71.76;H,10.49;N,5.40;S,6.18%];

4-ethylthio-3-hexadecanamido-N-(2-methylthioethyl)-

benzamide, in the form of white crystals, m.p. 92-94°C (from aqueous ethanol) [Elemental analysis:- C,66.5; H,9.7;N,5.5;S,12.5%; calculated:- C,66.09;H,9.51; N,5.51;S,12.60%];

4-ethylthio-3-heptadecanamido-N-(2-methylthioethyl)-benzamide, in the form of white crystals, m.p. 91-93°C (from aqueous ethanol) [Elemental analysis:- C,66.5; H,9.7;N,5.36;S,12.0%; calculated:- C,66.62;H,9.64; N,5.36;S,12.26%];

3-heptadecanamido-4-methylthio-N-(2-methylthioethyl)-benzamide, in the form of white crystals, m.p. 101-102°C (from aqueous ethanol and then from ethyl acetate) [Elemental analysis:- C,66.5;H,9.8;N,5.50; S,12.6%; calculated:- C,66.09;H,9.51;N,5.51;S,12.60%]; and

3-heptadecanamido-N-(2-methoxyethyl)-4-(methylthio)-benzamide, in the form of white crystals, m.p. 115-116°C (from aqueous ethanol and then from isopropanol) [Elemental analysis:- C,68.4;H,10.10; N,5.65;S,6.50%; calculated:- C,68.25;H,9.82;N,5.69; S,6.50%].

EXAMPLE 9

Compound W

By proceeding in a manner similar to that described in Example 2, but replacing the

N-(2-methoxy)ethyl-3-amino-4-(methylthio)benzamide by the appropriate quantity of 3-amino-N-butyl-4-(methylthio)benzamide and crystallising the product from toluene, there was prepared (Z)-N-butyl-3-octadec-9-enamido-4-(methylthio)benzamide, in the form of a soft, pale brown solid, m.p. 118-120°C [Elemental analysis:- C,71.3;H,10.0;N,5.59;S,6.37%; calculated:- C,71.66; H,10.02;N,5.57;S,6.38%].

EXAMPLE 10

Compounds X to AJ

By proceeding in a manner similar to that described in Example 5, but employing the appropriate acid chlorides and the appropriate anilines, there were prepared:-

4-ethylthio-N-(3-methylthiopropyl)-3-octadecanamido-benzamide, in the form of colourless crystals, m.p. 75-76°C (from a mixture of t-butyl methyl ether and methanol) [Elemental analysis:- C,67.4;H,10.0;N,5.0; S,11.6%; calculated:- C,67.59;H,9.88;N,5.08;S,11.64%];

4-ethylthio-3-heptadecanamido-N-(3-methylthiopropyl)-benzamide, in the form of white crystals, m.p. 74-77°C (from a mixture of t-butyl methyl ether and methanol) [Elemental analysis:- C,67.5;H,10.00;N,5.30;S,11.70%; calculated:- C,67.11;H,9.76;N,5.22;S,11.95%];

4-ethylthio-3-hexadecanamido-N-(3-methylthiopropyl)-

benzamide, in the form of white crystals, m.p. 75-78°C (from a mixture of t-butyl methyl ether and methanol) [Elemental analysis:- C,66.5;H,9.7;N,5.11;S,11.9%; calculated:- C,66.62;H,9.64;N,5.36;S,12.26%];
4-methylthio-N-(2-methylthioethyl)-3-octadecanamido-benzamide, in the form of white crystals, m.p. 104-106°C (from a mixture of t-butyl methyl ether and methanol) [Elemental analysis:- C,66.6;H,9.9;N,5.2; S,12.0%; calculated:- C,66.62;H,9.64;N,5.36;S,12.26%];
N-butyl-3-dodecanamido-4-methoxybenzamide, in the form of white crystals, m.p. 107-109°C (from t-butyl methyl ether) [Elemental analysis:- C,70.9;H,10.10;N,6.72%; calculated:- C,71.24;H,9.96;N,6.93%];
4-ethylthio-3-hexadecanamido-N-(3-methoxypropyl)-benzamide, in the form of white crystals, m.p. 78-80°C (from acetonitrile) [Elemental analysis:- C,68.4; H,9.93;N,5.1;S,6.21%; calculated:- C,68.73;H,9.94; N,5.53;S,6.33%];
N-butyl-3-octadecanamido-4-(methylthio)benzamide, in the form of a white powder, m.p. 115-118°C (from a mixture of t-butyl methyl ether and methanol) [Elemental analysis:- C,71.6;H,10.7;N,5.13;S,5.79%; calculated:- C,71.38;H,10.38;N,5.55;S,6.35%];
4-methylthio-N-(3-methylthiopropyl)-3-octadecanamido-benzamide in the form of a white powder, m.p. 87-94°C (from toluene) [Elemental analysis:- C,66.6;H,9.85;

N,4.83;S,11.65%; calculated:- C,67.12;H,9.76;N,5.22; S,11.94%];

4-ethylthio-N-(3-methoxypropyl)-3-octadecanamido-benzamide, in the form of a white powder, m.p. 80-83°C (from toluene) [Elemental analysis:- C,69.7;H,10.3; N,5.07;S,5.87%; calculated:- C,69.62;H,10.18;N,5.24; S,5.99%];

N-butyl-3-(5-chloropentanamido)-4-(ethylthio)benzamide, in the form of a white powder, m.p. 104-105°C (from t-butyl methyl ether) [Elemental analysis:- C,58.2; H,7.4;Cl,9.6;N,7.5;S,8.6%; calculated:- C,58.28;H,7.34; Cl,9.56;N,7.55;S,8.64%];

3-(4-chlorobutanamido)-4-ethylthio-N-(3-methylthio-propyl)benzamide in the form of a white powder, m.p. 80-81°C (from a mixture of t-butyl methyl ether and methanol) [Elemental analysis:- C,52.2;H,6.87;Cl,9.5; N,7.3;S,15.7%; calculated:- C,52.49;H,6.48;Cl,9.11; N,7.20;S,16.49%];

3-(5-chloropentanamido)-4-ethylthio-N-(3-methylthio-propyl)benzamide, in the form of a pale yellow powder, m.p. 95-96°C (from a mixture of t-butyl methyl ether and methanol) [Elemental analysis:- C,53.7;H,6.87; Cl,8.8;N,6.82;S,15.6%; calculated:- C,53.65;H,6.75; Cl,8.80;N,6.85;S,15.91%]; and

methyl 3-hexadecanamido-4-methoxybenzoate, in the form of colourless needles, m.p. 109-110°C (from ethanol)

[Elemental analysis:- C,71.1;H,9.9;N,3.26%; calculated:- C,71.56;H,9.85;N,3.34%].

EXAMPLE 11

Compounds AK and AL

By proceeding in a manner similar to that described in Example 7 but replacing the (Z)-methyl 4-methoxy-3-(octadec-9-enamido)benzoate by the corresponding quantity of methyl 3-hexadecanamido-4-methoxybenzoate (prepared as described in Example 10), there was prepared 3-hexadecanamido-4-methoxybenzoic acid, in the form of colourless needles, m.p. 198-200°C (from ethanol) [Elemental analysis:- C,71.1;H,9.8; N,3.40%; calculated:- C,71.07;H,9.69;N,3.45%], via sodium 3-hexadecanamido-4-methoxybenzoate.

EXAMPLE 12

Compound AM

A mixture of 3-hexadecanamido-4-methoxybenzoic acid (4.04g; prepared as described in Example 11) and thionyl chloride (1.3ml) was heated in boiling toluene (100ml) for 3 hours. The solvent was removed under reduced pressure. The residual acid chloride was dissolved in dry dichloromethane (35ml) and was added to a stirred solution of 2-methoxyethylamine (3ml) and dry triethylamine (1.6ml) in dichloromethane (115ml). After standing at the ambient temperature for 2 days, the solution was washed with hydrochloric acid

(2x200ml;2N) and then with water (2x200ml) and was then it was dried over potassium carbonate and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel, eluting with a mixture of diethyl ether and dichloromethane, to give 3-hexadecanamido-4-methoxy-N-(2-methoxyethyl)benzamide (2.0g), in the form of a white powder, m.p. 78-80°C [Elemental analysis:- C,69.8;H,10.3;N,5.90%; calculated:- C,70.09;H,10.02;N,6.06%].

EXAMPLE 13

Compound AN

A solution of 3-hexadecanamido-4-methoxybenzoyl chloride [prepared from 3-hexadecananamido-4-methoxy-benzoic acid (2.02g; prepared as described in Example 11) and thionyl chloride] in dichloromethane (50ml) was added to a stirred solution of 3-methylbut-2-enylamine hydrochloride (0.98g) in dichloromethane (100ml) and triethylamine (1ml). The mixture was stirred at the ambient temperature for 1 hour and was then washed succesively with water (100ml), aqueous sodium hydroxide solution (100ml;2N), dilute hydrochloric acid (100ml;2N) and with water (100ml), and it was then dried over magnesium sulphate and concentrated under reduced pressure . The resulting residue was chromatographed on silica gel, eluting with a mixture of methanol and dichloromethane, to give 3-hexadec-

anamido-4-methoxy-N-(3-methylbut-2-enyl)benzamide (0.6g), in the form of a cream solid, m.p. 109-111°C after crystallisation from a mixture of petrol (b.p. 40-60°C) and diethyl ether [Elemental analysis:- C,73.2;H,10.3;N,5.60%; calculated:- C,73.68;H,10.24; N,5.93%].

EXAMPLE 14

Compounds AO to AZ

A solution of 5,9-dioxahexadecanoyl chloride in dichloromethane [prepared from 5,9-dioxahexadecanoic acid (2.0g; prepared as described in Example 17) and oxalyl chloride (2.4ml) in dichloromethane (25ml)] was added to a stirred suspension of 3-amino-N-butyl-4-(methylthio)benzamide (1.83g) in dry dichloromethane (25ml) and triethylamine (2.5g), producing a clear solution. After standing at the ambient temperature for 65 hours, the solution was concentrated under reduced pressure to about 10ml. The residue was taken up in t-butyl methyl ether (300ml) and was washed sequentially with dilute hydrochloric acid (100ml; 0.5N), aqueous sodium hydroxide solution (100ml;2%w/v) and with dilute hydrochloric acid (100ml;0.5N) and was then dried and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel, eluting with ethyl acetate, to give N-butyl-4-

methylthio-3-(5,9-dioxahexadecanamido)benzamide (2.05g) in the form of a pale yellow, waxy solid [Elemental analysis:- C,65.4;H,9.6;N,5.93;S,6.42%; calculated:- C,64.96;H,9.23;N,5.83;S,6.67%].

By proceeding in a similar manner, but using the appropriate acids and the appropriate anilines, there were prepared:-

4-methylthio-N-(3-methylthiopropyl)-3-(5,9-dioxahexadecanamido)benzamide, in the form of a pale yellow, waxy solid [Elemental analysis:- C,61.0;H,8.9;N,5.36; S,12.4%; calculated:- C,60.90;H,8.65;N,5.46;S,12.51%];

N-butyl-4-ethylthio-3-(5,9,13-trioxahexadecanamido)-benzamide, in the form of an amber oil [Elemental analysis:- C,62.5;H,9.1;N,5.7;S,6.43%; calculated:- C,62.87;H,8.93;N,5.64;S,6.46%];

4-ethylthio-N-(3-methylthiopropyl)-3-(5,9-dioxahexadecanamido)benzamide, in the form of a pale yellow, waxy solid (eluting with a mixture of dichloromethane and methanol) [Elemental analysis:- C,61.4;H,8.91; N,5.34;S,12.0%; calculated:- C,61.56;H,8.80;N,5.32; S,12.17%];

N-butyl-4-ethylthio-3-(5,9-dioxahexadecanamido)-benzamide, in the form of a pale brown oil (eluting with a mixture of dichloromethane and methanol) [Elemental analysis:- C,65.4;H,9.6;N,5.5;S,6.26%; calculated:- C,65.55;H,9.37;N,5.66;S,6.48%];

4-ethylthio-N-(3-methoxypropyl)-3-(5,9-dioxahexadecanamido)benzamide, in the form of a pale brown oil (eluting with a mixture of dichloromethane and methanol) [Elemental analysis:- C,63.2;H,9.1;N,5.2; S,6.12%; calculated:- C,63.50;H,9.08;N,5.48;S,6.28%];

4-ethylthio-N-(3-methoxypropyl)-3-(5,9,13-trioxahexadecanamido)benzamide, in the form of a pale brown oil [Elemental analysis:- C,60.5;H,8.7;N,5.16;S,6.08%; calculated:- C,60.91;H,8.65;N,5.46;S,6.25%];

4-ethylthio-N-(3-methoxypropyl)-3-(5-oxahexadecanamido)benzamide, in the form of a pale brown oil that solidified on standing (eluting with a mixture of dichloromethane and methanol) [Elemental analysis:- C,66.4;H,9.8;N,5.35;S,6.24%; calculated:- C,66.10; H,9.51;N,5.51;S,6.30%];

4-methylthio-N-(3-methylthiopropyl)-3-(5-oxahexadecanamido)benzamide, in the form of a pale brown oil that solidified on standing (eluting with a mixture of dichloromethane and methanol) [Elemental analysis:- C,63.6;H,9.3;N,5.48;S,11.9%; calculated:- C,63.49;H,9.08;N,5.17;S,12.55%];

N-butyl-4-methylthio-3-(5-oxahexadecanamido)benzamide, in the form of a pale brown oil that solidified on standing (eluting with a mixture of dichloromethane and methanol) [Elemental analysis:- C,68.0;H,9.9;N,5.6; S,6.24%; calculated:- C,67.74;H,9.69;N,5.85;S,6.70%];

4-methoxy-N-(3-methylthiopropyl)-3-(5,9-dioxahexadecanamido)benzamide, in the form of a pale brown oil (eluting with a mixture of dichloromethane and methanol) [Elemental analysis:- C,62.5;H,9.2;N,5.48; S,6.19%; calculated:- C,62.87;H,8.93;N,5.64;S,6.46%]; and

4-ethylthio-N-(3-methylthiopropyl)-3-(5,9,13-trioxahexadecanamido)benzamide, in the form of a pale brown oil (eluting with a mixture of dichloromethane and methanol) [Elemental analysis:- C,58.2;H,8.5;N,4.96; S,11.3%; calculated:- C,59.06;H,8.39;N,5.30;S,12.13%].

EXAMPLE 15

Compound BA

Heptadecanoyl chloride (2.79g) was added dropwise during 10 minutes to a stirred solution of methyl 3-amino-4-(imidazol-1-yl)benzoate (2.0g; prepared as described in Reference Example 1) in dry pyridine (60ml). When the reaction was complete (judging by a thin-layer chromatogram), water (300ml) was added. The precipitated solid was collected, washed with water and dried and was then dissolved by heating in ethyl acetate (60ml) containing hydrochloric acid (1ml). The solid which crystallised on cooling was collected, was washed with diethyl ether and was dried at 80°C, to give methyl 3-heptadecanamido-4-

(imidazol-1-yl)benzoate in the form of white crystals of the hydrated hydrochloride, m.p. 106-109°C [Elemental analysis:- C,64.7;H,8.6;N,7.9;Cl,6.83;water, 3.8%; calculated for $C_{28}H_{43}N_3O_3.HCl.H_2O$:- C,64.72; H,8.99;N,7.81;Cl,6.59;water,3.35%].

EXAMPLE 16

Compounds BB to BG

By the application or adaptation of methods described hereinbefore, more especially in the preceding Examples, there were prepared:-
N-(3-methylsulphonylpropyl)-4-methylthio-3-(5,9-dioxahexadecanamido)benzamide, in the form of a pale brown oil which solidified on standing;
4-ethylthio-N-(3-methylthiopropyl)-3-(5,9-dioxaoctadecanamido)benzamide, in the form of a pale brown oil [Elemental analysis:- C,63.1;H,9.5;N,4.37%; calculated:- C,62.78;H,9.08;N,5.05%];
N-butyl-4-ethylthio-3-(5,10-dioxahexadecanamido)-benzamide, in the form of a pale yellow solid;
4-ethylthio-N-(3-methylthiopropyl)-3-(6,10,14-trioxahexadecanamido)benzamide, in the form of a pale brown oil [Elemental analysis:- C,58.0;H,8.5;N,5.30; S,11.0%; calculated:- C,59.06;H,8.39;N,4.95;S,12.13%];
4-imidazol-1-yl-N-(3-methylthiopropyl)-3-(5-oxahexadecanamido)benzamide, in the form of a white powder, m.p. 77-79°C [Elemental analysis:- C,66.0;H,8.9; N,10.7%; calculated:- C,65.62;H,8.74;N,10.56%]; and
3-hexadecanamido-4-imidazol-1-yl-N-(3-methylthiopropyl)benzamide, in the form of a white powder, m.p. 104-105°C [Elemental analysis:- C,68.6;H,9.4;N,10.7%; calculated:- C,68.14;H,9.15;N,10.60%].

EXAMPLE 17

Compounds INT a, INT b and INT c

Sodium bromite trihydrate (35.0g) was added to a cooled, vigorously stirred mixture of 5,9,13-trioxahexadecan-1-ol (11.5g), 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (0.25g), aqueous sodium hydrogen carbonate solution (450ml;5%w/v) and acetonitrile (450ml) maintaining a temperature of from 0°C to 10°C. The mixture was stirred at the ambient temperature for 4 hours and then the reaction was quenched by the careful addition of sufficient hydrochloric acid and aqueous sodium metabisulphite to give a pH of from 2 to 4 and to consume excess oxidant. The solution was extracted with t-butyl methyl ether (4x200ml) and the combined organic solution was washed with aqueous sodium chloride solution, dried and concentrated under reduced pressure. The resulting residue was distilled at an oven temperature of 170°C and a pressure of 0.1mmHg, to give 5,9,13-trioxahexadecanoic acid (10.3g) in the form of a colourless, mobile oil. [Elemental analysis:- C,59.52;H,9.99%; calculated:- C,59.9;H,10.9%].

By proceeding in a similar manner, but replacing the 5,9,13-trioxahexadecan-1-ol by the appropriate quantities of 5,9-dioxahexadecan-1-ol and 5-oxahexa-

decan-1-ol, respectively, and with the difference that the residue left after concentrating under reduced pressure was taken up in t-butyl methyl ether, filtered to remove solids, and concentrated under reduced pressure again before distilling, there were prepared:- 5,9-dioxahexadecanoic acid, in the form of a colourless, mobile oil [Elemental analysis:- C,64.9; H,11.3%; calculated:- C,64.58;H,10.84%]; and 5-oxahexadecanoic acid, in the form of a colourless, mobile oil which solidified, m.p. 28-30°C [Elemental analysis:- C,68.5;H,11.6%; calculated:- C,69.72;H,11.70%].

EXAMPLE 18

Compounds INT d, INT e and INT f

By proceeding in a manner similar to that described in Example 17, but using the appropriate alcohols, there were prepared:-

6,10,14-trioxahexadecanoic acid, in the form of a colourless, mobile oil [Elemental analysis:- C,57.5; H,10.0%; calculated:- C,59.52;H,9.99%];

5,10-dioxahexadecanoic acid, in the form of a colourless, mobile oil, b.p. 97-105°C/0.1mmHg [Elemental analysis:- C,66.1;H,11.5%; calculated:- C,64.58;H,10.84%]; and

5,9-dioxahexadecanoic acid, in the form of a colourless, mobile oil [Elemental analysis:- C,66.2; H,11.4%; calculated:- C,66.63;H,11.18%].

REFERENCE EXAMPLE 1

Methyl 4-(imidazol-1-yl)-3-nitrobenzoate (19.3g) was reduced by reaction with iron powder (22.0g) in boiling ethanol (150ml) containing water (35ml) and hydrochloric acid (1.5ml;1N). Recrystallisation from ethyl acetate gave methyl 3-amino-4-(imidazol-1-yl)-benzoate (9.7g) in the form of pale yellow crystals, m.p. 161-165°C.

REFERENCE EXAMPLE 2

Methyl 4-fluoro-3-nitrobenzoate (17.0g) was reacted with imidazole (13.0g) at the ambient temperature in dry tetrahydrofuran (100ml), to give methyl 4-(imidazol-1-yl)-3-nitrobenzoate (14.68g) in the form of large yellow needles, m.p. 71-74°C (from t-butyl methyl ether).

REFERENCE EXAMPLE 3

4-Ethylthio-N-(3-methoxypropyl)-3-nitrobenzamide (47.0g) was reduced by reaction with iron powder (55.0g) in boiling ethanol (750ml) containing hydrochloric acid (95ml;0.5N). Recrystallisation from t-butyl methyl ether gave 3-amino-4-ethylthio-N-(3-methoxypropyl)benzamide (32.4g) in the form of fine cream needles, m.p. 73-75°C.

REFERENCE EXAMPLE 4

Reaction of 3-methoxypropylamine with 4-ethylthio-3-nitrobenzoyl chloride and

recrystallisation from toluene gave 4-ethylthio-N-(3-methoxypropyl)-3-nitrobenzamide in 74% yield in the form of a yellow solid, m.p. 101-103°C.

REFERENCE EXAMPLE 5

A solution of 3-(3-propoxypropoxy)propan-1-ol (25.39g) and dry pyridine (11.47g) in dichloromethane (30ml) was added during 10 minutes to a stirred solution trifluoromethanesulphonic anhydride (49.1g) in dichloromethane (90ml), keeping the temperature below 0°C. The mixture was stirred for 3 hours without further cooling and was then washed with ice-cold water (100ml) and dried. The solution was filtered, diluted with dichloromethane (150ml) and was then stirred with potassium carbonate (27.0g) and 4-hydroxybutyl acrylate (25.2g) overnight at ambient temperature under an atmosphere of argon. The mixture was then heated at reflux for 8 hours. The mixture was filtered, the residue was washed with dichloromethane (300ml) and the filtrate was then washed with hydrochloric acid (250ml;1N) and with water (2x250ml). The residue left after drying and concentrating under reduced pressure was dissolved in ethanol (300ml) and was stirred with a solution of sodium hydroxide (11.4g) in water (65ml) for 4 hours. The solution was concentrated under reduced pressure to

about 180ml, was diluted with t-butyl methyl ether (1litre) and was washed with water (2x400ml). The residue left after drying and concentrating under reduced pressure was distilled under reduced pressure to give 5,9,13-trioxahexadecan-1-ol (16.9g) in the form of a colourless, mobile oil, b.p. 109-113°C/0.1mmHg.

By proceeding in a similar manner, but using the appropriate quantity of 3-heptyloxypropan-1-ol instead of 3-(3-propoxypropoxy)propan-1-ol, there was prepared 5,9-dioxahexadecan-1-ol, in the form of a colourless, mobile oil, b.p. 123-125°C/0.1mmHg.

REFERENCE EXAMPLE 6

Lithium aluminium hydride (3.5g) was carefully added to a stirred solution of aluminium chloride (38.98g) in diethyl ether (200ml) under a gentle stream of nitrogen, keeping the temperature below 15°C. The mixture was stirred for 2 hours and then 2-decyl-1,3-dioxepane (30.7g) was added during 30 minutes. The mixture was stirred at reflux for 8 hours and was then cooled to ambient temperature. Water (50ml) was added dropwise, followed by diethyl ether (300ml). The aqueous fraction was extracted with diethyl ether (3x200ml) and the combined organic solution was then dried. The solvent was removed and the residue was distilled, to give 5-oxahexadecan-1-ol (25.24g) in the form of an oil, b.p. 126-127°C/0.1mmHg.

The present invention also includes within its scope pharmaceutical formulations which comprise at least one of the compounds of formula I, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier or coating. In clinical practice the compounds of the present invention may be administered parenterally, rectally or orally.

Solid compositions for oral administration include compressed tablets, pills, powders and granules. In such solid compositions, one or more of the active compounds is, or are, admixed with at least one inert diluent such as starch, sucrose or lactose. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents, such as magnesium stearate.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water and liquid paraffin. Besides inert diluents such compositions may comprise adjuvants, such as wetting and suspending agents, and sweetening, flavouring, perfuming and preserving agents. The compositions according to the invention for oral administration also

include capsules of absorbable material such as gelatin, containing one or more of the active substances with or without the addition of diluents or excipients.

Preparations according to the invention for parenteral administration include sterile aqueous, aqueous-organic, and organic solutions, suspensions and emulsions. Examples of organic solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil and injectable organic esters such as ethyl oleate. The compositions may also contain adjuvants such as stabilising, preserving, wetting, emulsifying and dispersing agents. They may be sterilised, for example, by filtration through a bacteria-retaining filter, by incorporation in the compositions of sterilising agents, by irradiation or by heating. They may also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula I.

The percentage of active ingredient in the compositions of the invention may be varied, it being

necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from about 0.5 to about 70, preferably about 1 to about 10, mg/kg body weight per day by oral administration.

The following Example illustrates pharmaceutical compositions according to the present invention.

COMPOSITION EXAMPLE 1

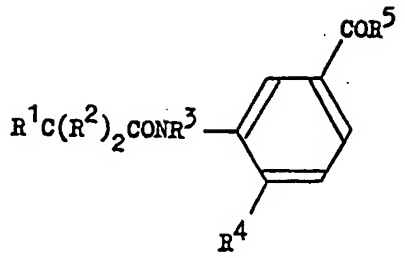
No. 2 size gelatin capsules each containing:-

N-butyl-3-hexadecanamido-4-(methylthio)-benzamide;	20 mg
lactose	100 mg
starch	60 mg
dextrin	40 mg
magnesium stearate	1 mg

were prepared in accordance with the usual procedure.

CLAIMS

1. A benzamide derivative of the formula:



I

wherein R^1 represents a straight- or branched-chain alkyl group containing up to 20 carbon atoms, optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms, and optionally interrupted by one or more sulphinyl or sulphonyl groups, optionally carrying one or more substituents selected from halogen atoms, amino groups, alkoxy, alkylthio and alkylamino groups each containing up to 3 carbon atoms and groups of the formula $-CONR^6R^7$ wherein R^6 represents a hydrogen atom or a methyl group and R^7 represents a methyl, trifluoromethyl or trichloromethyl group, the symbols R^2 are the same or different and each represents a hydrogen atom, a straight- or branched-chain alkyl group containing up to 6 carbon atoms or an optionally substituted phenyl group or the two groups R^2 together with the carbon atom to which they are attached form a saturated or unsaturated ring containing from 3 to 8

carbon atoms and optionally containing one or more hetero atoms selected from oxygen, sulphur and nitrogen atoms, R^3 represents a hydrogen atom or a straight- or branched-chain alkyl group containing up to 6 carbon atoms, R^4 represents a straight- or branched-chain alkoxy or alkylthio group containing up to 6 carbon atoms or a dimethylamino group or a 5- to 8-membered heterocyclo group containing at least one nitrogen atom and linked via that nitrogen atom to the rest of the molecule, and R^5 represents a group of the formula $-NR^8R^9$ or $-OR^{10}$ wherein R^8 and R^9 may be the same or different and each represents a hydrogen atom or a straight- or branched-chain alkyl group containing up to 10 carbon atoms, optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms, and optionally interrupted by one or more sulphinyl or sulphonyl groups, and R^{10} represents a hydrogen atom or a straight- or branched-chain alkyl group containing up to 10 carbon atoms, optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms, and optionally interrupted by one or more sulphinyl or sulphonyl groups, and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 wherein R^1 represents an alkylthioalkyl, alkylaminoalkyl or dialkylaminoalkyl group.

3. A compound according to claim 1 wherein R^1 represents an alkyl, alkenyl, alkoxyalkyl, alkoxyalkoxyalkyl or alkoxyalkoxyalkoxyalkyl group.

4. A compound according to any one of the preceding claims wherein the heterocyclo group represented by R^4 is an imidazol-1-yl or pyrrolidin-1-yl group.

5. A compound according to claim 1 wherein at least one of the symbols has a value selected from the following:-

(i) R^1 represents an alkyl, alkenyl, alkoxyalkyl, alkoxyalkoxyalkyl, alkoxyalkoxyalkoxyalkyl or haloalkyl group, containing from 8 to 20 carbon atoms;

(ii) the symbols R^2 each represent a hydrogen atom, or the two groups R^2 together with the carbon atom to which they are attached form a cycloalkyl ring containing from 3 to 8 carbon atoms;

(iii) R^3 represents a hydrogen atom;

(iv) R^4 represents an imidazol-1-yl group or a straight- or branched-chain alkoxy or alkylthio group containing up to 3 carbon atoms;

(v) R^8 represents a hydrogen atom or a straight- or branched-chain alkyl group containing up to 3 carbon atoms;

(vi) R^9 represents a straight- or branched-chain alkyl or alkenyl group containing up to 6 carbon atoms,

optionally interrupted by one or more oxygen or sulphur atoms or sulphonyl groups;

(vii) R^{10} represents a hydrogen atom or a straight- or branched-chain alkyl group containing up to 6 carbon atoms, the other symbols being as defined in claim 1.

6. A compound according to claim 5 wherein

(i) R^1 represents an alkyl or alkenyl group containing from 8 to 20 carbon atoms;

(ii) the cycloalkyl ring represented by the two groups R^2 together with the carbon atom to which they are attached contains 5 or 6 carbon atoms;

(iv) the alkoxy or alkylthio group represented by R^4 contains 1 or 2 carbon atoms;

(v) R^8 represents hydrogen or methyl;

(vi) R^9 represents an alkyl, alkoxyalkyl or alkylthioalkyl group containing 3 or 4 carbon atoms or an alkenyl group containing 5 carbon atoms;

(vii) R^{10} represents a hydrogen atom or a straight- or branched-chain alkyl group containing up to 3 carbon atoms.

7. A compound according to claim 5 or 6 wherein

(i) R^1 represents an alkyl or alkenyl group containing from 10 to 18 carbon atoms;

(ii) the cycloalkyl ring represented by the two groups

R^2 together with the carbon atom to which they are attached contains 5 carbon atoms;

(iv) the alkoxy or alkylthio group represented by R^4 is methoxy, methylthio or ethylthio;

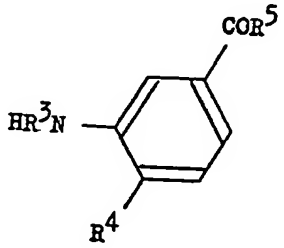
(vi) R^9 represents a butyl, methoxyethyl, methylthioethyl, methoxypropyl, methylthiopropyl, methylsulphonylpropyl or methylbut-2-enyl group;

(vii) R^{10} represents a hydrogen atom or a methyl group.

8. A benzamide derivative according to claim 1 hereinbefore identified as any one of compounds A to BG or a pharmaceutically acceptable salt thereof.

9. A process for the preparation of a compound according to claim 1 which comprises:

(A) the reaction of a compound of the general formula:



II

wherein R^3, R^4 and R^5 are as defined in claim 1, with a compound of the general formula :

$$R^1\text{-}C(R^2)_2COZ^1 \qquad \text{III}$$

wherein R^1 and R^2 are as defined in claim 1 and Z^1

represents a halogen atom or an alkoxycarbonyloxy group, or with the corresponding anhydride of the general formula :

$$[R^1\text{-}C(R^2)_2CO]_2O \qquad IV$$

wherein R^1 and R^2 are as defined in claim 1, or

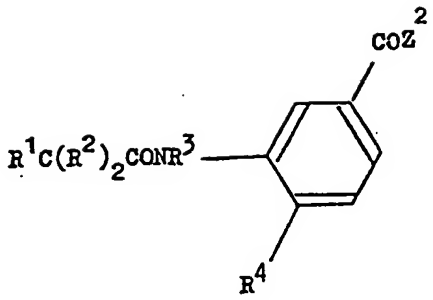
(B) when R^5 is other than a group OR^{10} in which R^{10} is hydrogen, the reaction of a compound of general formula :

$$R^{11}OH \qquad V$$

wherein R^{11} represents a straight- or branched-chain alkyl group containing up to 10 carbon atoms, optionally containing one or more carbon-carbon double or triple bonds, and optionally interrupted by one or more hetero atoms, and optionally interrupted by one or more sulphinyl or sulphonyl groups, or a compound of general formula :

$$HNR^8R^9 \qquad VI$$

wherein R^8 and R^9 are as defined in claim 1, with a compound of the general formula :



VII

wherein R^1, R^2, R^3 and R^4 are as hereinbefore defined and Z^2 represents a hydroxy group, a halogen atom or an alkoxycarbonyloxy group, or with the corresponding anhydride;

(C) optionally followed by the conversion by known methods of a compound of general formula (I) into another compound of general formula (I)

(D) optionally followed by conversion into a pharmaceutically acceptable salt.

10. A pharmaceutical composition which comprises a benzamide derivative of general formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier or coating.

11. A pharmaceutical composition useful in the treatment of a condition which can be ameliorated by an inhibitor of acyl coenzyme-A:cholesterol-O-acyl transferase which comprises a benzamide derivative of general formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically

acceptable carrier or coating.

12. A method for the treatment of a condition which can be ameliorated by an inhibitor of acyl coenzyme-A:cholesterol-O-acyl transferase which comprises the administration of a benzamide derivative of general formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof.

13. A compound of the general formula:

$$R^{12}\text{-}C(R^2)_2COOH \qquad IX$$

wherein R^{12} represents an alkoxyalkyl, alkoxyalkoxyalkyl or alkoxyalkoxyalkoxyalkyl group and R^2 is as defined in claim 1.

14. A process for the preparation of a compound as claimed in claim 13 which comprises the oxidation of a compound of the general formula :

$$R^{12}\text{-}C(R^2)_2CH_2OH \qquad X$$

wherein R^2 is as defined in claim 1 and R^{12} is as defined in claim 13, to convert the group $-CH_2OH$ to a group -COOH.